L5 ANSWER 1 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2004:41451 USPATFULL

TITLE: Keratinocyte growth factor-2

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PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6693077	B1	20040217
APPLICATION INFO.:	US 2000-610651		20000630 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-345373, filed on 1 Jul 1999 Continuation of Ser. No. US 1998-23082, filed on 13 Feb 1998, now patented, Pat. No. US 6077692

Continuation-in-part of Ser. No. US 1997-910875, filed on 13 Aug 1997 Continuation-in-part of Ser. No. US 1997-862432, filed on 23 May 1997 Division of Ser. No. US 1995-461195, filed on 5 Jun 1995 Continuation-in-part of Ser. No. WO 1995-US1790, filed on 14 Feb 1995 Continuation-in-part of Ser. No. US 610651 Continuation-in-part of Ser. No. US 1996-696135, filed on 13 Aug 1996 Continuation-in-part of Ser. No. US 1995-461195, filed on 5 Jun 1995 Continuation-in-part of Ser. No. WO 1995-US1790, filed on 14 Feb 1995

NUMBER	DATE

L41 ANSWER 13 OF 13 USPATFULL on STN
ACCESSION NUMBER: 90:46192 USPATFULL
TITLE: Intraocular prostheses
INVENTOR(S): Caldwell, Delmar R., 1430 Tulane Ave., New Orleans, LA,
United States 70112
Jacob-Labarre, Jean T., 2020 Gravier St., Suite B, New Orleans, LA, United States 70112-2234

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4932968		19900612
APPLICATION INFO.:	US 1989-391887		19890809 (7)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1987-70783, filed on 7 Jul 1987, now patented, Pat. No. US 4865601
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Apley, Richard J.
ASSISTANT EXAMINER: Prizant, James
LEGAL REPRESENTATIVE: Pravel, Gambrell, Hewitt, Kimball & Krieger
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 885

DETD . . . prosthesis 56 has been manipulated into the position, the pupil
may be made to contract by using for example an **acetylcholine** solution, the anterior chamber washed using for example 0.9% sterile saline solution and reformed using healon, and the incision may. . .

DETD . . . of the zonule fiber action, when they stretch and relax, is to change the curvature of the lens. When the **ciliary** muscle is relaxed, the zonules are under **tension**. The **tension** of the zonule fibers pulls the lens capsule and lens toward their equator so that the thickness of the lens is decreased or flattened. When the **ciliary** muscle contracts, the **tension** on the zonules relaxes. In turn, the tension on the lens capsule and lens relaxes. When the zonule fibers relax. . .

```
                E ASTHENOPIA/CT
L1           783 S E3-E29

     FILE 'EMBASE, USPATFULL, CAPLUS, IPA, BIOSIS, MEDLINE' ENTERED AT
     17:24:54 ON 28 SEP 2004
L2          1749 S ASTHENOPIA OR L1
L3        792891 S (ANIMAL MODEL##) OR (EXPERIMENTAL MODEL##) OR
(LAB###########
L4            17 S L2 AND L3
L5            16 DUPLICATE REMOVE L4 (1 DUPLICATE REMOVED)
L6            17 S L3 (20W) L2
L7        725169 S ANIMAL MODEL##
L8         80745 S EXPERIMENTAL MODEL####
L9          6847 S LAB############ MODEL###
L10           15 S L7 (20W) L2
L11         1075 S ASTHENOPIA
L12            0 S L11 (20W) L7
L13            1 S L11 (20W) L8
L14            0 S L11 (20W) L9
L15      5380163 S MODEL#####
L16            5 S L11 (20W) L15
L17            4 DUPLICATE REMOVE L16 (1 DUPLICATE REMOVED)

=> s magnus (20w) apparatus
L18           38 MAGNUS (20W) APPARATUS

=> s l2 and l18
L19            1 L2 AND L18

=> d l19

L19 ANSWER 1 OF 1  USPATFULL on STN
AN     2003:112839  USPATFULL
TI     Experimental model and method for evaluation of therapeutic agents
       against asthenopia
IN     Katsuyama, Iwao, Osaka, JAPAN
PI     US 2003077571      A1   20030424
AI     US 2002-92210      A1   20020306 (10)
PRAI   JP 2001-130414      20010426
       JP 2002-50116       20020226
DT     Utility
FS     APPLICATION
LN.CNT 996
INCL   INCLM: 435/004.000
       INCLS: 435/325.000
NCL    NCLM:  435/004.000
       NCLS:  435/325.000
IC     [7]
       ICM: C12Q001-00
       ICS: C12N005-06
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> s l18 and ciliary
L20            1 L18 AND CILIARY

=> s l18 and muscle#
L21           22 L18 AND MUSCLE#
```

=> duplicate remove l21
DUPLICATE PREFERENCE IS 'EMBASE, USPATFULL, CAPLUS, BIOSIS, MEDLINE'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L21
L22 19 DUPLICATE REMOVE L21 (3 DUPLICATES REMOVED)

=> s l22 and (acetylcholine or serotonin or histamine or muscarine or nicotine or endothelin or 5ht or ach)
L23 9 L22 AND (ACETYLCHOLINE OR SEROTONIN OR HISTAMINE OR MUSCARINE OR NICOTINE OR ENDOTHELIN OR 5HT OR ACH)

=> d 1-9 ibib kwic

L23 ANSWER 1 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 74013869 EMBASE
DOCUMENT NUMBER: 1974013869
TITLE: Pharmacologic studies on 3',4' dideoxykanamycin B (DKB) (Japanese).
AUTHOR: Koeda T.; Shibata U.; Asaoka H.; et al.
CORPORATE SOURCE: Cent. Res. Lab., Meiji Seika Kaisha, Ltd., Yokohama, Japan
SOURCE: Japanese Journal of Antibiotics, (1973) 26/1 (28-39).
CODEN: JJANAX
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
LANGUAGE: Japanese
AB . . . vessels dilated slightly following the administration of 10% DKB.
The movements of the isolated rabbit intestine and rat uterus in **Magnus' apparatus** were inhibited by the administration of 0.005% DKB. The tonus of the isolated guinea pig trachea strip chain in **Magnus' apparatus** was relaxed by the administration of 0.01% DKB. These effects of DKB were antagonized by the addition of BaCl2 and **acetylcholine**. The responses of the phrenic nerve diaphragm preparation of rat to nerve stimulation were blocked by the administration of 0.3%. . . effect of DKB was antagonized by the addition of CaCl2 and pentobarbital. At high concentrations of DKB, irritability of the **muscle** of rat was observed, and permeability of skin vessels was enhanced by the administration of 10% DKB. In vivo no. . .
CT Medical Descriptors:
*blood pressure
*blood vessel permeability
*body temperature
*central nervous system
*circulation
*diaphragm
*drug screening
*electrocardiography
*heart rate
*intestine
*intestine motility
***muscle**
*nervous system

*phrenic nerve
*prothrombin time
*breathing
***smooth muscle**
*trachea
*uterus
*uterus contractility
intravenous drug administration
rat
guinea pig
theoretical study
***acetylcholine**
*antigen
*atropine
*dibekacin
*diphenhydramine
*kanamycin
*propranolol

RN (**acetylcholine**) 51-84-3, 60-31-1, 66-23-9; (atropine) 51-55-8, 55-48-1; (dibekacin) 34493-98-6, 58580-55-5; (diphenhydramine) 147-24-0, 58-73-1; (kanamycin) 11025-66-4, 61230-38-4, 8063-07-8; (propranolol) 13013-17-7, 318-98-9, 3506-09-0,. . .

L23 ANSWER 2 OF 9 USPATFULL on STN

ACCESSION NUMBER:	2003:112839 USPATFULL		
TITLE:	Experimental model and method for evaluation of therapeutic agents against asthenopia		
INVENTOR(S):	Katsuyama, Iwao, Osaka, JAPAN		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003077571	A1	20030424
APPLICATION INFO.:	US 2002-92210	A1	20020306 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	JP 2001-130414		20010426
	JP 2002-50116		20020226
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	BROWN & MICHAELS, PC, 400 M & T BANK BUILDING, 118 NORTH TIOGA ST, ITHACA, NY, 14850		
NUMBER OF CLAIMS:	18		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	4 Drawing Page(s)		
LINE COUNT:	996		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . experimental model and method for evaluating and screening drugs or quasi-drugs against asthenopia, including accommodative asthenopia, by preparing a ciliary **muscle** sample enucleated from a non-human animal, inducing contraction by one or more of contraction stimulants, measuring the contraction rate of the ciliary **muscle**, treating it with a test formulation and measuring the contraction rate of the ciliary **muscle** after such treatment.

SUMM [0006] Ciliary **muscle** is a smooth **muscle** which makes up the major segment of the ciliary body surrounding the eye lens in ocular tissues. Asthenopia, in particular accommodative asthenopia, is defined as a difficulty in eye lens adjustment associated with fatiguing

of the ciliary **muscle**; Journal of Japanese Ophthalmology Association vol. 92, 1854-1858(1988). The ciliary **muscle**, when stimulated, undergoes isometric contraction, i.e., it contracts without a change in length of the **muscle** itself, and fatiguing of the ciliary **muscle** is reflected by declining tension during muscular contraction and a delay in the contraction/relaxation process. Therefore, one of the appropriate. . . so-called "Magnus" type directly observes the change in tension of muscular contraction and delay of the contraction/relaxation process using ciliary **muscle** suspended in a Magnus tube.

SUMM [0007] **Magnus** methods are usually carried out by use of a **Magnus apparatus** which is mainly comprised of: (1) a Magnus tube of about 1-2 cm in diameter and about 2-5 cm in. . . influences of other organs and yet it does not loose its mobility due to the nerve plexus remaining in the **muscle**.

SUMM [0008] Known Magnus methods include the study of the M3-type muscarinic receptor in the ciliary **muscle** of the cow (Hiroshi Matsuda et al: Gen. Pharmac., 30 (4), 579-584 (1998)), and the study of the relaxation response to nitrous oxide in the ciliary **muscle** of the cow (Soichiro Kamiawa et al: Exp. Eye Res., 66, 1-7 (1998)), (Hiroshi Masuda et al: Current Eye Res.,. . . Alternatively, the Magnus system can be used to evaluate the relaxation effect of eye drops on the contraction of ciliary **muscle** induced by **endothelin**-1 (Japan patent publication No. H09-59173), or by potassium chloride or carbachol (Japan patent publication No. H07-133225). However, these KNOWN magnus methods evaluate only the preventive effects of medicines against transient contraction of ciliary **muscle** induced by endotherin-1, potassium chloride or Carbachol, these making the use of said particular chemical compounds questionable in magnus methods. . . vitro a Magnus method combined with the use of the above compounds does not necessarily replicate the fatiguing of ciliary **muscle** that occurs in asthenopia in vivo.

DRWD [0010] FIG. 1 shows a preliminary test for measuring the contraction rate of ciliary **muscle** in vitro upon stimulation by **acetylcholine**. Contraction of ciliary **muscle** was induced by the addition of **acetylcholine**, and the contraction rate was determined as a function of the number of stimulations. Before the tenth stimulation, varying concentrations. . .

DRWD [0011] FIG. 2 shows a graph showing a comparison of the contraction rate of ciliary **muscle** for different doses of cyanocobamin in a preliminary test.

DRWD [0012] FIG. 3 shows a graph showing changes in contraction rate of ciliary **muscle** as a function of stimulation by **acetylcholine** in a final test. At the tenth stimulation, varying concentrations of cyanocobalamin were added.

DRWD [0013] FIG. 4 shows a graph showing a comparison of the contraction rate of ciliary **muscle** for different doses of cyanocobalamin in a final test.

DETD . . . there is provided an experimental model of asthenopia, wherein said asthenopia is caused by inducing repeated contractions of the ciliary **muscle** derived from a non-human test animal until said ciliary **muscle** exhibits a substantially stable decrease in the

tension of muscular contraction.

DETD . . . According to still another aspect of the invention, there is provided an experimental model of asthenopia in which the ciliary **muscle** is enucleated from a non-human mammalian animal or from a fowl.

DETD . . . According to a further aspect of the invention, there is provided an experimental model of asthenopia in which the ciliary **muscle** is contracted a plurality of times by the use of smooth **muscle** contraction-inducing means.

DETD [0018] According to still another aspect of the invention, there is provided an experimental model of asthenopia wherein the smooth **muscle** contraction-inducing means is a chemical stimulant, preferably through not necessarily selected from the group consisting of **acetylcholine, serotonin, histamine, muscarine, nicotine** and **endothelin.**

DETD [0019] According to another aspect of the invention, there is provided an experimental model of asthenopia wherein the smooth **muscle** contraction-inducing means is an electrical stimulant.

DETD . . . of the invention, there is provided an experimental model of asthenopia, such as described above, wherein the contraction of ciliary **muscle** is repeated at least three times to give a substantially stable decrease in the tension of muscular contraction.

DETD . . . the further aspects of the invention, there is provided an experimental model of asthenopia as described above wherein the ciliary **muscle** shows a decrease of 50.+-.30% in the tension of muscular contraction, or decrease of 50.+-.20% in the tension of muscular. . .

DETD . . . method of preparing an experimental model of asthenopia, which comprises the step of inducing repeated contractions in vitro of ciliary **muscle** taken from a non-human test animal until the ciliary **muscle** exhibits a substantially stable decrease in the tension of muscular contraction.

DETD . . . invention, there is provided a method for evaluating a therapeutic agent against asthenopia comprising the steps of contacting the ciliary **muscle** from a non-human animal with said agent, and measuring the effect on the contraction of said ciliary **muscle.**

DETD [0025] This evaluation can be carried out by the use of a **Magnus apparatus.**

DETD [0026] The ciliary **muscle** to be used in this in vitro model of asthenopia is obtained by enucleation from non-human test animals. Examples of. . .

DETD [0027] The animals, before being subjected to enucleation of the ciliary **muscle,** are preferably bred under well-controlled conditions to obtain consistent preparations of the ciliary **muscle.** After enucleation, the ciliary **muscle** may preferably be cut to an appropriate size in order to obtain a biological sample. The size of the organ. . .

DETD [0028] Contraction of the enucleated ciliary **muscle** should be done a plurality of times in order to give a substantially stable decrease in the tension of the muscular contraction. Any smooth **muscle** contraction-inducing means, i.e., any stimuli to induce the reversible contraction of smooth **muscle,** may be used for this purpose. For example, the contraction may be induced either by physical stimuli, chemical stimuli, or electrical stimuli. Suitable

examples of chemical stimuli include **acetylcholine, serotonin, histamine, muscarine, nicotine, endothelin,** and the like. These stimuli may be used either individually or in any combination. Among them, **acetylcholine** is preferably used, since it is a naturally occurring stimulant which stimulates the cholinergic receptor to induce smooth **muscle** contraction, being liberated from the parasympathetic nerve.

DETD [0029] **Serotonin** is an effective intracerebral chemical transmitter and normally exists in the intestinal chromaffin cells of the intestinal mucosa. It moves into blood platelets from the chromaffin cells and induces contraction in vascular smooth **muscle** or in smooth **muscles** such as enucleated intestinal canal and muscularis of the bronchus during pulmonary circulation.

DETD [0030] **Histamine** is stored in basophils in the blood and in tissue mast cells and plays a leading role in inflammation and. . . dilation, accentuation and permeability accentuation of minute capillary blood vessels. It also induces a strong contraction of bronchus and smooth **muscle**, e.g., in blood vessels.

DETD [0031] **Muscarine** is an alkaloid of the toadstool origin and, like **acetylcholine**, stimulates the cholinergic receptor, which can be blocked by atropine. It acts on postsynaptic membranes and induces the strong contraction of bronchus and smooth **muscle**, e.g., in blood vessels.

DETD [0032] **Nicotine** is an alkaloid obtained from tobacco leaves, like **acetylcholine**, and stimulates cholinergic receptors, which can be blocked by hexamethonium. It acts on the neuromuscular synapses of autonomic ganglia and motor end plates, and induces a strong contraction of bronchus and smooth **muscle**, e.g., in blood vessels. Because of these activities, **nicotine** is preferred to use in this invention.

DETD [0033] **Endothelin** is also preferred as a chemical stimulant because **endothelin**, a polypeptide of 21 amino acids produced by human or pig epithelial cells, induces the strong contraction of blood vessels. . .

DETD . . . the above stimulants are different from each other in their mechanisms of action, they all induce contraction in the smooth **muscle** of the bronchus, blood vessels and the intestinal canal. They also induce the contraction of smooth ciliary **muscle**. The concentration of the chemical stimulants to be used in the practice of this invention may be selected based on. . .

DETD . . . For the present invention, a suitable combination of these conditions may be readily decided based on the degree of ciliary **muscle** contraction to be obtained, for example, making reference to the conditions described in Masuda et al's Gen. Pharmac. 30, 579-584(1998),. . .

DETD . . . from the control of central nerves, does not loose its mobility because of the nerve plexus which remains in the **muscle** tissue. When the experiment is carried out by a Magnus method, the Magnus tube is filled with a conventional nutrient. . .

DETD [0037] In practice, a sample of ciliary **muscle** as described above is suspended in the Magnus tube with a loading weight using a tensile transducer, and the first stimulation is preferably given thirty

minutes after suspension to induce **muscle** contraction. In treatment a chemical stimulant, such as atropine, is used as the smooth **muscle** contraction-inducing means, it is preferred that the stimulant be added to the nutrient solution so that the final concentration of. . . times, preferably 3 to 20 times, and most preferably 4 to 15 times. A high level fatiguing of the ciliary **muscle** may be achieved by such repetitive stimulations, but stimulation of more than 50 times may give no substantially additional benefit.. . .

DETD [0040] It is preferred that the ciliary **muscle** sample which, after repeated stimulations thereof, shows a stable decrease of 50.+-.30%, more preferably 50.+-.20% decrease, and most preferably 50.+-.10%. . .

DETD . . . most preferably 50.+-.10% decrease, in tension of muscular contraction is used as a standard sample for subsequent experiments using the **Magnus apparatus**.

DETD [0045] Since the same sample of ciliary **muscle** can be used to test multiple medicines, it is possible to compare various drugs without influence by specimen-to-specimen variations.

DETD [0049] Each enucleated eyeball was sclerotomized and amputated to half at the equatorial position, and then the ciliary **muscle** was carefully ablated from the sclera after removal of the crystalline lens. The ciliary **muscle** thus obtained was cut into a strip of 3 mm in width and 6 mm in length and used in. . .

DETD [0050] The ciliary **muscle** obtained in EXAMPLE 1 was suspended in a Magnus tube filled with Krebs-Henseleit solution bubbled through with a mixed gas. . .

DETD . . . transducer (Isometric Transducer, FD Pick-up TB-611 T type, made by Nihon Kohden Corporation, Tokyo, Japan). After equilibration for 30 minutes, **acetylcholine** (made by SIGMA, St. Louis, Mo.) at a final concentration of 10-4 mol/L was added for the first stimulation. After. . .

DETD . . . the sample in the Magnus tube was treated with atropine at a final concentration of 10-6 mol/L and subjected to **acetylcholine** stimulation as described above, in order to confirm whether the tension of the sample was in fact due to stimulation by **acetylcholine**. The results are shown in Tables 6-8.

No. of measureing	Average of Contraction Rate (%) .+-. standard deviation
2nd	86.4 .+-.. . .

DETD [0063] As seen in Tables 1-5 and in FIG. 1, fatiguing of the ciliary **muscle** occurs upon stimulation by **acetylcholine**. The contraction rate decreases as repeated stimulations by **acetylcholine** are applied. It is evident from Tables 6-8 that the contraction occurs via the muscarinic receptor, since contraction of the ciliary **muscle** is elicited by **acetylcholine** and inhibited by atropine.

DETD . . . results in Table 9 and FIG. 3 and FIG. 4, the test formulation had an anti-fatiguing effect on the ciliary **muscle**. The effect of the test formulation was higher than the vehicle formulation without

cyanocobalamin. Comparison of the test formulation and the standard formulation shows that they have a similar level of anti-fatiguing effect on the ciliary **muscle**.

DETD . . . an experimental model for evaluating or screening a medicine which shows an antagonistic effect on the transient contraction of ciliary **muscle** induced by chemical stimulation, but not for evaluating the therapeutic effect on asthenopia, because asthenopia is not necessarily ascribed to such transient ciliary **muscle** contractions. In addition, that known in vitro model simply provides a screening method to evaluate the preventive effect of a medicine on **muscle** contraction by contacting or treating the ciliary **muscle** with the medicine before inducing the ciliary **muscle** contraction. In contrast, the experimental model and method of the present invention involves repeated contractions of ciliary **muscle** which give a stable decrease in the tension of muscular contraction, thus replicating the fatiguing of ciliary **muscle** which occurs in asthenopia, and hence this invention is much more advantageous for use in evaluating the therapeutic effect of. . . asthenopia. According to the present invention, the therapeutic effect of the medicine is evaluated after the fatigue of the ciliary **muscle** is induced. Thus, the same sample of ciliary **muscle** can be used to test multiple medicines, which enables persons engaged in this art to compare various medicines without the.

CLM What is claimed is:

. . . the effect of a medicine against asthenopia, wherein said asthenopia is caused by inducing repeated contraction in vitro of ciliary **muscle** from a non-human animal until said ciliary **muscle** shows a substantially stable decrease in the tension of muscular contraction.

3. The experimental model of claim 1, wherein the ciliary **muscle** has been derived from a non-human mammal or fowl.

4. The experimental model of claim 2, wherein the ciliary **muscle** has been derived from a non-human mammal or fowl.

5. The experimental model of claim 3, wherein the ciliary **muscle** has been enucleated from a non-human mammal.

6. The experimental model of claim 4, wherein the ciliary **muscle** has been enucleated from a non-human mammal.

7. The experimental model of claim 1, wherein the ciliary **muscle** is contracted a plurality of times by the use of smooth **muscle** contraction-inducing means.

8. The experimental model of claim 7, wherein the smooth **muscle** contraction-inducing means comprise a chemical stimulant.

9. The experimental model of claim 8, wherein the chemical stimulant is selected from the group consisting of **acetylcholine**, **serotonin**, **histamine**, **muscarine**, **nicotine** and **endothelin**.

10. The experimental model of claim 7, wherein the smooth **muscle** contraction-inducting means comprises an electrical stimulant.

11. The experimental model of claim 1, wherein the contraction of ciliary **muscle** is repeated at least three times to give a substantially stable decrease in the tension of muscular contraction.

12. The experimental model of claim 1, wherein said ciliary **muscle** shows a decrease of 50.+-.30% in the tension of muscular contraction.

13. The experimental model of claim 1, wherein said ciliary **muscle** shows a decrease of 50.+-.20% in the tension of muscular contraction.

14. The experimental model claim 1, wherein said ciliary **muscle** shows a decrease of 50.+-.10% in the tension of muscular contraction.

. . . model for evaluating the effect of a medicine against asthenopia, which comprises the step of inducing repeated contractions of ciliary **muscle** derived from a non-human animal until said ciliary **muscle** shows a substantially stable decrease in the tension of muscular contraction.

16. A method for evaluating a medicine against asthenopia, comprising the steps of contacting the ciliary **muscle** from a non-human animal in the experimental model of claim 1 with said medicine, and measuring the effect of said medicine on the contraction of said ciliary **muscle**.

18. The method claimed of claim 16, carried out with use of a **Magnus apparatus**.

L23 ANSWER 3 OF 9 USPATFULL on STN

ACCESSION NUMBER:	1999:159491 USPATFULL
TITLE:	Dihydrophenanthrene
INVENTOR(S):	Kubo, Michinori, Sakai, Japan Yoshikawa, Masayuki, Minoo, Japan Matsuda, Hideaki, Habikino, Japan Matsuda, Hisashi, Kyoto, Japan Murakami, Toshiyuki, Kyoto, Japan Shimada, Hiromi, Toyonaka, Japan Sakurama, Tetsuo, Osaka, Japan Nomura, Manabu, Miyazaki-gun, Japan
PATENT ASSIGNEE(S):	Nomura Co., Ltd., Miyazaki, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5997874		19991207
APPLICATION INFO.:	US 1998-30730		19980225 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1996-661970, filed on 12 Jun 1996, now patented, Pat. No. US 5750107 which is a continuation-in-part of Ser. No. US 167828		

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1997-113304	19970325

JP 1997-113305 19970325
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Weber, Jon P.
ASSISTANT EXAMINER: Hanley, Susan
LEGAL REPRESENTATIVE: Sheridan Ross P.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 401
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The compounds of the present invention have a variety of physiological properties including reducing the amount of smooth **muscle** contraction and causing relaxation of smooth **muscles**. Therefore, they can be used in a variety of application including as a vasodilator.

DETD This example illustrates relaxation of **muscles** and inhibition of **muscle** contraction by calanthenol.

DETD The experiment was conducted using thoracic aorta **muscles** from rats according to the procedure by Magnus. Briefly, the Magnus procedure involves placing a tissue in a Magnus appratus. . . typically 95% oxygen and 5% carbon dioxide. One end of the tissue is attached to a fixed point of the **Magnus apparatus** and the other end of the tissue is attached to a force transducer which is used to measure the tension. . .

DETD Tension (T.sub.1)of the **muscle** tissue was measured using a **Magnus apparatus** after addition of a test component, **serotonin** (5 to 10 M) and norepinephrine (6 to 10 M) to the **muscle** tissue. Tension (T.sub.0) was measured using the same procedure without a test component. Percent **muscle** contraction inhibition is defined as:

DETD The results of the **muscle** contraction inhibition test are shown in Table 1.

DETD The ability of calanthenol to cause **muscle** relaxation was also measured by the following experimental procedure.

DETD Thoracic aorta **muscle** tissues from rats were placed on a **Magnus apparatus** and treated with 50 mM KCl solution and the tension of the tissue was measured (T'.sub.0) . A test component was added and the tension was again measured (T'.sub.1). Percent **muscle** relaxation was calculated by the following formula:

DETD % **muscle** relaxation=[(T'.sub.0 -T'.sub.1)/T'.sub.0].times.100

DETD The results of % **muscle** relaxation test are also shown in Table 1.

DETD TABLE 1

Test component	% **muscle** contraction inhibition		% **muscle** relaxation
Concentration	**serotonin**	norepinephrine	KCl
Calanthenol			
10.sup.-4 M	62	23	79

MeOH extract
50 .mu.g/ml
7 0 0
EtOAc layer
50 .mu.g/ml
30 0 24
H.sub.2 O. . .
DETD As shown in Table 1, calanthenoL prevents **muscle** contraction and causes relaxation of **muscles**. Therefore, the novel class of dihydrophenanthrene compound of the present invention including calanthenol and derivatives thereof can be used as. . .

L23 ANSWER 4 OF 9 USPATFULL on STN

ACCESSION NUMBER:	89:4617 USPATFULL		
TITLE:	Isoquinoline derivatives		
INVENTOR(S):	Hidaka, Hiroyoshi, Tshu, Japan Morikawa, Anri, Narashino, Japan		
PATENT ASSIGNEE(S):	Asahi Kasei Kogyo Kabushiki Kaisha, Osaka, Japan (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4798897		19890117
APPLICATION INFO.:	US 1987-40828		19870421 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Raymond, Richard L.		
ASSISTANT EXAMINER:	Turnipseed, James H.		
LEGAL REPRESENTATIVE:	Finnegan, Henderson, Farabow, Garrett & Dunner		
NUMBER OF CLAIMS:	13		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2491		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . derivatives. More particularly, the present invention is concerned with isoquinoline derivatives which are novel compounds that affect the vascular smooth **muscle** of a mammal, thereby being of value as, e.g., vasodilators, cerebral circulation ameliorators, and drugs for prevention and treatment of. . . cardiovascular thrombosis, hypertonia and other circulatory organ diseases. The isoquinoline derivatives of the present invention also affect the bronchial smooth **muscle** of a mammal, thereby being valuable drugs for prevention and treatment of respiratory organ diseases such as asthma.

SUMM . . . and other circulatory organ diseases. Moreover, it has unexpectedly been found that these novel compounds also exert an excellent smooth **muscle** relaxation action on the bronchus and, hence, are valuable drugs for the prevention and treatment of respiratory organ diseases such. . .

SUMM . . . vessel diseases such as angina and myocardial infarction. Moreover, the isoquinoline derivatives of the present invention exert an excellent smooth **muscle** relaxation action on bronchial tubes, which action is not exerted by the known compounds. Accordingly these isoquinoline derivatives are also. . .

SUMM . . . effectively increase the diameter of blood vessels, especially a coronary artery, and exert an excellent relaxation action on the smooth **muscle** of a blood vessel, an excellent blood flow increasing action and an antihypertensive acion. Hence, they can be

advantageously utilized. . . cardiovascular thrombosis, hypertonia, and other circulatory organ diseases. Moreover, the compounds of the present invention also exert an excellent smooth **muscle** relaxation action on bronchial tubes, which action is not exerted by known cerebrovascular compounds. Accordingly, these compounds are also valuable. . .

SUMM The above-mentioned relaxation action on the smooth **muscle** of a blood vessel was confirmed by the relaxation of the mesenteric artery of a rabbit in accordance with the. . . femoral arteries in accordance with the method described later. The above-mentioned relaxation action on bronchial tubes was confirmed through the **histamine** contraction inhibition action on bronchial tubes removed from a guinea pig.

SUMM . . . given later shows that the strong action is exerted by the compounds of the present invention. For example, in the **histamine** contraction inhibition test using bronchial tube samples from a guinea pig, 1-(5-isoquinolinesulfonyl)-3-aminopiperidine [Compound (63)] exhibited ED.sub.50 value, i.e. a concentration. . .

DETD 3. Inhibition of **Histamine** Contraction of Bronchial Tubes (Relaxation of Bronchial Tubes)

DETD The relaxation action of the compounds of the present invention on the smooth **muscle** of bronchial tubes was examined by means of **Magnus apparatus** according to the "Method Of Using Bronchial Tubes Taken Out From Guinea Pigs" (K. Takagi and H. Ozawa, "Experimental Techniques. . . 20-ml bath filled with Krebs-Henseleit nutrient solution and maintained at a temperature of 37.degree. C. To the bath was added **histamine** so that the **histamine** concentration became 10 .mu.M, causing the bronchial tube sample to contract. After the contraction became stable, the compounds of the. . . Measurement was made of concentrations (ED.sub.50) of the compounds which attained 50% decrease of the contraction caused by 10 .mu.M **histamine**.

L23 ANSWER 5 OF 9 USPATFULL on STN

ACCESSION NUMBER:	77:69332 USPATFULL		
TITLE:	Preparation of piperidinyl-alkyl-benzamides		
INVENTOR(S):	Roll, William D., Toledo, OH, United States		
PATENT ASSIGNEE(S):	The University of Toledo, Toledo, OH, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4035373		19770712
APPLICATION INFO.:	US 1976-660652		19760223 (5)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Milestone, Norma S.		
LEGAL REPRESENTATIVE:	Purdue, John C.		
NUMBER OF CLAIMS:	5		
EXEMPLARY CLAIM:	1		
LINE COUNT:	260		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . dioxide asphyxiation (guinea pigs). Strips of uterus and ileum approximately 1 cm.in length were immediately excised and suspended in a **Magnus** bath **apparatus** of volume 75 cc. which was maintained at 37.degree. C. and through which air was constantly

bubbled. The rat ileum. . .

DETD . . . the chain was assured by monitoring its response to sequential additions of isoproterenol HCl (Isuprel HCl solution) 0.1 percent** and **histamine** dihydrochloride solution 0.1 percent.

DETD . . . animal. Blood pressure was determined by direct carotid artery cannulation and was recorded by means of a mercury manometer and **muscle** lever tracing on a kymograph. Drugs were injected i.p. at intervals no shorter than 5 minutes.

DETD An aqueous solution of N-(4-piperidnylmethyl)-m-trifluoromethylbenzamide hydrochloride (0.1 percent: dosage 0.2 cc.) antagonized the effect of an **acetylcholine** chloride solution in distilled water (0.1 percent: 0.1 cc. dosage) on the rat ileum. Atropine can also be used to antagonize the effect of the **acetylcholine** chloride solution, but atropine, alone, has no relaxant effect on this tissue. Isoproterenol antagonizes the effect of **acetylcholine** chloride solution on the rat ileum and, as indicated above, also has a relaxant effect.

DETD . . . dosage 0.2 cc.) caused a relaxant effect on guinea pig ileum; this dose also antagonized the stimulant effect of a **serotonin** creatinine sulfate monohydrate solution in distilled water (0.1 percent: dosage 0.05 cc.) and of a **histamine** dihydrochloride solution in distilled water (0.1 percent: dosage 0.05 cc.).

L23 ANSWER 6 OF 9 USPATFULL on STN

ACCESSION NUMBER: 76:55771 USPATFULL

TITLE: 1,4-Dihydropyridine derivatives

INVENTOR(S): Murakami, Masuo, Tokyo, Japan
Takahashi, Kozo, Tokyo, Japan
Iwanami, Masaru, Yokohama, Japan
Fujimoto, Masaharu, Tokyo, Japan
Shibanuma, Tadao, Asaka, Japan
Kawai, Ryutaro, Shiraoka, Japan
Takenaka, Toichi, Tokyo, Japan

PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 3985758		19761012
APPLICATION INFO.:	US 1975-584268		19750606 (5)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1974-442781, filed on 15 Feb 1974, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1973-25566	19730303
	JP 1973-52307	19730511
	JP 1973-83276	19730724
	JP 1973-134070	19731129
	JP 1973-20423	19730220
	JP 1973-44821	19730420

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Rotman, Alan L.

LEGAL REPRESENTATIVE: Burgess Ryan and Wayne

NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
LINE COUNT: 1443
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Methods: Isolated guinea-pig ileum was suspended in Tyrodes solution by use of **Magnus apparatus** and the movements of the **muscle** were recorded in a kymograph by an isotonic lever. Barium chloride, acetylchloline and **histamine** were used as an agonist and 50% inhibition by the antagonist was measured regarding the contractile responses to the antagonist.
DETD Table

Antagonist	Concentration (g/ml)	Spasmolytic activity (g/ml.+-.S.E) Papaverine	Nifedipine	Compound A
BaCl.sub.2	2.times.10.sup.-.sup.4	7.2.+-.0.2.times.10.sup.-.sup.6	3.3.+-.0.2.times.10.sup.-.sup.9	1.9.+-.0.4.times.10.sup.-.sup.9
Acetylchloline	10.sup.-.sup.7	1.1.+-.0.1.times.10.sup.-.sup.5	1.6.+-.1.1.times.10.sup.-.sup.8	5.2.+-.10.times.10.sup.-.sup.9
Histamine	10.sup.-.sup.7	7.0.+-.1.9.times.10.sup.-.sup.6	5.5.+-.0.9.times.10.sup.-.sup.8	1.8.+-.0.2.times.10.sup.-.sup.9

L23 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1956:41717 CAPLUS
DOCUMENT NUMBER: 50:41717
ORIGINAL REFERENCE NO.: 50:8054c-e
TITLE: Pharmacological studies on the photosensitizing dye, T7, an aminovinyl compound. II
AUTHOR(S): Maesawa, Tadao
CORPORATE SOURCE: Kumamoto Univ. Med. Coll.
SOURCE: Kumamoto Medical Journal (1955), 8, 101-8
CODEN: KUMJAX; ISSN: 0023-5326
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Small intestine excised from a 2 kg. unanesthetized rabbit, divided into 2-3 cm. lengths was suspended in a modified **Magnus apparatus** containing 50 ml. Tyrode's soln. T7 had an excitant effect on smooth **muscle** at a weak concn. of less than 1:200,000 and a paralytic action on the **muscle** at concns. greater than 1:200,000. The stimulating action of T7 was not influenced by atropine applied previously either at weak or strong concns., which indicated no relation of T7 to the parasympathetic nervous system and the Auerbach plexus. The depressing action of adrenaline was not influenced by previous application of T7, which suggested that the latter has no

relation to the depressing fibre ending of the sympathetic nerve. Barium chloride and physostigmine were found to co-operate with T7 at weak concentration, which indicated the action of the latter to be due to direct stimulation on the smooth **muscle**. The intestinal actions of pilocarpine and **acetylcholine** appeared also after T7 administration, which demonstrated that T7 does not paralyze the parasympathetic nerve ending.

L23 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1953:48835 CAPLUS
DOCUMENT NUMBER: 47:48835
ORIGINAL REFERENCE NO.: 47:8252c-d
TITLE: Action of sparteine on the dynamics of the uterine horn of the rat
AUTHOR(S): Dirner, Z.; Thuranszky, K.
CORPORATE SOURCE: Univ. Szeged
SOURCE: Acta Physiologica Academiae Scientiarum Hungaricae (1952), 3, 601-9
CODEN: APACAB; ISSN: 0001-6756
DOCUMENT TYPE: Journal
LANGUAGE: German
AB A neutral soln. of sparteine sulfate elicits automatic contractions of the uterine horn of albino rats when the movements have ceased. Existing movement is accentuated. Sparteine increases in the **Magnus apparatus** tonus as well as amplitudes. The effect is obtained even if the organ is stretched by excessive pull. The work of the **muscle** is augmented several 100%. The uterus horn of castrate rats is of low sensitivity to sparteine and **acetylcholine**. By induction of a cycle with dienestrol the uterus obtains a normal responsiveness.

L23 ANSWER 9 OF 9 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1989:395602 BIOSIS
DOCUMENT NUMBER: PREV198937062250; BR37:62250
TITLE: AUTOMATIC **MAGNUS APPARATUS** FOR ESTIMATION OF THE CONTRACTILE RESPONSE IN ISOLATED SMOOTH **MUSCLE**.
AUTHOR(S): KITAGAWA H [Reprint author]; IZUMITA M; KOHEI H
CORPORATE SOURCE: DEP PHARMACOL, NIPPON BOEHRINGER INGELHEIM, KAWANISHI 666-01, JPN
SOURCE: Japanese Journal of Pharmacology, (1989) Vol. 49, No. SUPPL, pp. 281P.
Meeting Info.: 62ND GENERAL MEETING OF THE JAPANESE PHARMACOLOGICAL SOCIETY, KYOTO, JAPAN, MARCH 25-28, 1989.
JPN J PHARMACOL.
CODEN: JJPAAZ. ISSN: 0021-5198.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 22 Aug 1989
Last Updated on STN: 29 Aug 1989
TI AUTOMATIC **MAGNUS APPARATUS** FOR ESTIMATION OF THE CONTRACTILE RESPONSE IN ISOLATED SMOOTH **MUSCLE**.
IT Miscellaneous Descriptors
ABSTRACT GUINEA-PIG **ACETYLCHOLINE** THORACIC AORTA ILEUM DRUG INJECTION COMPUTER

RN 51-84-3 (**ACETYLCHOLINE**)

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	180.30	182.95

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.40	-1.40

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 17:45:19 ON 28 SEP 2004